REMARKS/ARGUMENTS

Applicant provides herewith an amendment to the claims. Support for the amendment is found in the specification, and is discussed further below. Applicant submits that no new matter has been added by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

The present communication is fully responsive to the Final Office Action dated June 19, 2006. Applicant also acknowledges and responds herein to the faxed communication from the Examiner dated December 18, 2006.

The Office Action dated June 19, 2006, included rejections based on alleged anticipation (35 U.S.C. §102) and alleged obviousness (35 U.S.C. §103). The present Response with Amendment is fully responsive to each of the Examiner's points in that Office Action. Applicant reiterates the arguments made in the prior Responses, and in particular, in the Response filed on December 22, 2005. Applicant believes that all claims in their present form are novel and non-obvious. Any amendment to the claims as provided herein does not represent an acquiescence to any rejection made by the Examiner in any Office Action or to any position taken by the Examiner. Applicant traverses all rejections to the extent that they may be applied to the claims following entry of the present amendment. Applicant respectfully requests reconsideration of the claims in view of the amendments and remarks herein.

THE STATUS OF THE CLAIMS

Claims **1-22** and **24-50** are pending with entry of this amendment. Claims **1, 24-26, 30, 35, 36, 38-40, 49** and **50** are amended herein. Claims **23** and **51-57** were previously cancelled. This amendment to the claims introduces no new matter. Support for the amendment is found in the specification as originally filed. These amendments are made without prejudice and are not to be construed as abandonment of any subject matter subject matter or agreement with any objection or rejection of record.

35 U.S.C. §102

In the Office Action dated June 19, 2006, the Examiner maintained the rejection of claims **25-27, 33, 34, 37-45** and **50** (based on their dependency from claim **25**) under 35

U.S.C. §102(e) as allegedly anticipated by Dooley *et al.* (U.S. Patent No. 6,635,423). Applicant respectfully disagrees, and traverses this rejection.

In order for a reference to anticipate a claim, the reference must teach each and every element of the claim. As previously discussed in the prior Responses, Dooley *et al.*, does not meet this requirement. The novel features of the invention are specifically and sufficiently recited in the independent claim **25** to distinguish the present invention over Dooley *et al.* Neither claim **25** nor any claim that depends from claim **25** is anticipated by Dooley *et al.*

The invention provides novel, inverted microarray configurations distinct from Dooley *et al.*

The present application recites methods for quantitating expression products in biological sample RNA, where the methods use *arrayed (immobilized) nucleic acid samples that are isolated directly from the biological sample RNA, or are enzymatic products that use the expressed biological sample RNA as their synthesis template.* Thus, any nucleic acid arrayed on the immobilized substrate has a corresponding expression product in the expressed RNA sample. Furthermore, the arrays are then interrogated with a plurality of unique probes, *each capable of producing a different detectable signal.*

The invention described in the specification requires elements that are not employed in classical microarray formats (which includes the "informative nucleic acid arrays" described by Dooley *et al*). For example, the present invention uses heterologous products generated directly from the biological sample RNA *to array on the immobilized phase.* Furthermore, the invention requires a plurality of defined sequence probes that are *each uniquely labelled to produce distinct detectable signals* to interrogate the array. Dooley *et al.* does not teach these limitations. In Dooley *et al.,* single nucleic acid species are used to construct the classical array, and a pool of *uniformly-labelled* expression products are used to interrogate the classical array.

In the Office Action, the Examiner states that the expression "selective amplification" has no special meaning and does not narrow the breadth of the claim (see Office Action, page 6, paragraphs 2-4). Applicants point out that the methods of the present invention further require *arraying* the nucleic acids selectively amplified from the RNA samples. Dooley *et al.* does not array nucleic acids amplified from the RNA samples being analyzed.

The Examiner states that Dooley *et al.* discloses an array, where the nucleic acid sequences on the array "are derived from (*i.e.*, corresponding to) differentially expressed RNAs," (see Office Action, page 6, paragraphs 3 and 4). Applicant disagrees with the Examiner's characterization of Dooley *et al.* The expression "derived from" as used by Dooley *et al.* refers to an analytical process (*i.e.*, a ranking) that is used to prioritize which nucleic acid sequences should be arrayed on an "informative array." In Dooley *et al.*, the data obtained from standard nucleic acid arrays are used to derive which expressed genes are relevant to a certain biological process. Nucleic acids corresponding to only those genes of interest are synthesized and used to construct an "informative" nucleic acid array. In Dooley *et al.*, the actual RNA sample (or, *e.g.*, corresponding cDNA or other amplified product) remains in the soluble phase and is used to hybridize to the array. In contrast, the present invention uses nucleic acids physically derived from and corresponding to the RNA samples to construct an array.

Another feature that distinguishes the present invention from Dooley *et al.* is the use of a plurality of distinctly labelled probes *that can be differentiated from each other by different detectable signals* following probing of the array. Dooley *et al.* does not teach this feature. Applicants point out that the sample nucleic acids of Dooley *et al.* are not used to construct an array (in Dooley *et al.*, they are labelled and used in the soluble phase to hybridize to an array).

The Examiner states that the expression "defined sequence probes," is allegedly insufficient to distinguish the claim from the methods described in Dooley *et al.* (see Office Action, page 7, 2nd and 3rd paragraphs). In his statement, the Examiner fails to note that each defined sequence probe must also be capable of generating a different detectable signal. Dooley is deficient in that feature.

Independent Claim 25 is Not Anticipated by Dooley et al.

In the present Office Action, the Examiner alleges that the language used in claim **25** might be broadly interpreted to encompass Dooley *et al.* For example, the Examiner states that the word "corresponding" is allegedly ambiguous in describing the source of the arrayed amplified nucleic acids (see Office Action, page 6, top paragraph). Applicant respectfully disagrees.

Solely for the purpose of advancing the prosecution of the present application, and without acquiescing to the rejection, Applicant has amended claim **25**. This amendment removes the term "corresponding to," thereby removing any alleged ambiguity in the source of the arrayed material. The arrayed material in claim 25 is now referred to as "selectively amplified nucleic acid samples." The selectively amplified nucleic acid samples (to be arrayed) are amplified directly from the RNA samples (step c). Dooley *et al.* does not teach nucleic acids that are amplified directly from an RNA sample that are used to generate an array.

Further, amended claim 25, step (c) requires that the selectively amplified nucleic acid samples that are used to generate the array comprise a plurality of species. In contrast, the nucleic acids that are used in Dooley *et al.* to construct the arrays are single species at each addressable location.

Applicant notes that claim 25 requires that the plurality of defined sequence probes used to analyze the arrays are each capable of generating a detectable signal that can be differentiated from the other detectable signals from the remaining probes. Dooley et *al.* does not teach the use of multiple uniquely labelled probes to analyze an array.

As used in the amended claim **25**, the present specification provides ample support for "selective amplification" and "selectively amplified nucleic acid samples." See, for example, the specification at paragraphs 12, 62, 73, 110-112, 116-125 and 197-201. The specification as filed also provides ample support for "a signal corresponding to hybridization" as used in claim **25**. See, for example, the specification at paragraphs 21, 22 and 158-169.

In view of the arguments above, and the amendment to the claims, Applicant asserts that claim **25** in its present form is novel. The Examiner also rejected claims that are dependent on claim **25**. If an independent claim is novel, so must each claim that depends upon the independent claim also be novel, as each dependent claim contains all of the limitations found in the independent claim. Applicant asserts that all claims are novel, and requests that this rejection be withdrawn and all claims passed to allowance.

35 U.S.C. §103(a)

In the Office Action dated June 19, 2006, the Examiner maintained the rejection of claim **1**, and dependent claims **2-13, 15-22, 24, 26, 27, 30-45** and **47-50** under 35 U.S.C. §103(a) as allegedly obvious and unpatentable over Dooley *et al.* (U.S. Patent No. 6,635,423) in view of Lockhart *et al.* (International Publication WO 97/10365). The Examiner also maintained his rejection of claims 14, 28, 29 and 46 under 35 U.S.C. §103(a) over Dooley *et al.* and further in view of various combinations of Lockhart *et al.*, Cho *et al.*, (*Proc. Natl. Acad. Sci. USA* 98(17):9819-9823 [August 14, 2001]), Nilsen *et al.*, (U.S. Patent No. 6,046,038) and Shuber (U.S. Patent No. 5,882,856). In total, all pending claims were rejected under 35 U.S.C. §103(a). Where the rejected dependent claims are multiple dependent claims, the rejection is based on dependency on claim **1**.

Applicant respectfully disagrees, and traverses this rejection. A *prima facie* case of obviousness requires that the prior art reference(s) must teach each limitation of the claims. The combination of the cited art, taken with the general knowledge in the field, must provide all of the elements of the claimed invention. Contrary to the Examiner's statements, Dooley *et al.*, or any combination of Dooley *et al.* with features from any of the references cited by the Examiner fail this test. Applicant reasserts that the claims as filed are novel and non-obvious.

Dooley *et al.* (alone or in combination with supplemental references) is deficient

As discussed extensively above, and in the previously filed Responses, Applicants have described the salient features of the invention. That is, the claimed invention uses a non-traditional microarray configuration, where the normal sample/probe relationship is inverted. In this novel configuration, a plurality of nucleic acid samples corresponding to expressed RNA samples are affixed onto an array (*e.g.*, a solid phase support surface). This array is then probed (*i.e.*, used in a hybridization reaction) with a plurality of soluble phase probes of defined sequence, where each probe comprises a distinct label. This novel approach is emphasized throughout the specification, and is most clearly described in paragraphs 0036-0038 and 0216-0218.

An inverted microarray format, as taught by the present specification, is not taught in Dooley *et al.*, Lockhart *et al.*, nor by any other combination of references cited by the Examiner. The nucleic acids that are arrayed in Dooley *et al.* are not derived from an RNA

sample as described in the present application. The expression "derived from" as used by Dooley *et al.* refers to an analytical process that is used to prioritize which nucleic acid sequences should be arrayed on an "informative array." In contrast, the nucleic acids used to construct an array of the present invention are physically derived from and correspond to the RNA samples.

Further distinguishing the present invention, the claimed methods require a plurality of probes to hybridize with the array, where each probe is capable of generating a different detectable signal. Neither Dooley, nor any other reference cited by the Examiner, teaches this.

The Claims are Non-Obvious

In the Office Action dated June 19, 2006, the Examiner states that the expression "plurality of nucleic acids *corresponding to* the plurality of expressed RNA samples" as used in claim 1, step (c) may allegedly be insufficient to exclude Dooley *et al.* (see the Office Action, page 14, 4th paragraph; and pages 17-18). Applicant disagrees.

The Examiner also raises issue with the limitation "defined sequence probe" as used in claim **1**. The Examiner alleges that this feature is taught by Dooley *et al.* Applicant points out that the Examiner fails to consider that each defined sequence probe must also be capable of generating a different detectable signal. Dooley *et al.* is deficient in that feature. All labelled probes used in Dooley *et al.* are uniformly labelled with the same detectable signal.

Nonetheless, solely for the purpose of advancing the prosecution of the present application, and without acquiescing to the rejection, Applicant has amended claim **1**. This amendment removes any alleged lack of clarity in the source of the nucleic acid being arrayed. The nucleic acid samples being arrayed, as described in amended step (c), are now explicitly defined as:

(i) total cellular RNA or a subset thereof isolated from said biological samples (for support, see the specification at paragraphs 10, 44, 82, 105-125 and 190);

(ii) mRNA isolated from said biological samples (for support, see the specification at paragraphs 10, 44, 82, 105-125 and 190);

(iii) cDNA produced from i or ii (for support, see the specification at paragraphs 10, 44, 46, 73, 105-125 and 190); and

(iv) nucleic acids amplified from i, ii or iii (for support, see the specification at paragraphs 10, 12, 47, 105-125 and 190).

Furthermore, it is now explicitly stated in step (c) that each nucleic acid sample comprises a plurality of different nucleic acid species. This is clearly the case when using total cellular RNA, mRNA or cDNA. Selectively amplified nucleic acids, *e.g.*, produced in multiplex rtPCR reactions to yield at least two amplified species, also meet this requirement. For support, see the specification at paragraphs 12, 117, 118, 138 and 197. The nucleic acids that are used in Dooley *et al.* to construct the arrays are single nucleic acid species at each addressable location on the array.

Applicants have also amended dependent claims **24, 26, 30, 35, 36, 38-40, 49** and **50**. These amendments are solely to improve readability, make the claim language in the dependent claims consistent with the amended language of independent claims **1** and 25, and to reflect proper antecedents.

In view of the arguments above, and the amendment to the claims, Applicant asserts that the presently amended claim **1** is non-obvious. The Examiner also rejected all claims that are dependent on claim **1**. If an independent claim is non-obvious, it follows that each claim that depends upon the independent claim is also non-obvious. Applicant requests that tihs rejection be withdrawn and the claims be passed to allowance.

FAXED COMMUNICATION DATED DECEMBER 18, 2006

The Examiner provided a faxed communication to the Applicant on December 18, 2006. In that communication, the Examiner requested clarification of locations of support for "mRNA" as recited in claim 1, step (c). Applicant points to the discussion above as well as support previously discussed in the Supplemental Response filed on March 30, 2006 (see page 10 in that Response).

CONCLUSION

In view of the foregoing, Applicant believes that all claims now pending in this application are in condition for allowance. If the Examiner believes there are any remaining issues regarding the patentability of the pending claims, the Examiner is encouraged to contact the undersigned by telephone to expedite the issuance of a Notice of Allowance.

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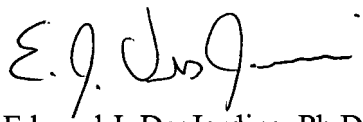
Respectfully submitted,



Edward J. DesJardins, Ph.D.
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Attachements:

1) A petition to extend the period of response for **three** months;
2) A transmittal sheet;
3) A fee transmittal sheet;
4) A RCE transmittal; and,
5) A receipt indication postcard.